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A Phase I study of AD5-GUCY2C-PADRE in stage I and II colon cancer patients

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Background

Ad5-GUCY2C-PADRE is a replication-deficient human type 5 recombinant adenovirus (Ad5) vaccine encoding guanylyl cyclase C (GUCY2C) fused to the PAn DR Epitope (PADRE). GUCY2C, a paracrine hormone receptor producing the second messenger cyclic GMP (cGMP), is selectively expressed by intestinal epithelial cells and a subset of hypothalamic neurons, but not other tissues. Importantly, GUCY2C is over-expressed in nearly all primary and metastatic human colorectal tumors. Preclinical studies in mice demonstrated selective tolerance of GUCY2C-specific CD4+ T cells, but not CD8+ T or B cells, necessitating inclusion of the exogenous CD4+ T helper cell epitope PADRE to maximize GUCY2C-specific CD8+ T cell and antibody responses and antitumor efficacy, without autoimmunity.

Patients and methods

This is an open-label, single arm "proof-of-concept" study evaluating a single dose level of Ad5-GUCY2C-PADRE as a vaccine for surgically-treated, node-negative colon cancer subjects (NCT01972737). Patients received a single intramuscular administration of 10^{11} Ad5-GUCY2C-PADRE viral particles. Safety and immunomonitoring where examined at 30, 90 and 180 days following vaccination. Primary objectives were to determine the safety, tolerability and toxicity of Ad5-GUCY2C-PADRE and to determine whether Ad5-GUCY2C-PADRE induces GUCY2C-specific immune responses. The study employed a joint efficacy-toxicity design and included stopping rules for either efficacy or toxicity. Results here were obtained during the planned interim analysis following accrual of 10 subjects.

Results

The vaccine was well tolerated, producing only mild adverse events (AEs). Short-lived injection site pain/swelling, body aches and chills were the most commonly observed AEs and occurred in 30-40% of subjects. GUCY2C-specific antibody and T-cell responses were observed in a subset of subjects. Consistent with preclinical mouse data, T-cell responses were composed of CD8+, but not CD4+, T cells. Importantly, GUCY2C-specific responses occurred only in subjects with low Ad5 neutralizing antibody (NAb) titers at the time of vaccination, suggesting that pre-existing Ad5 immunity limits Ad5-GUCY2C-PADRE immunogenicity.

Conclusions

Interim analysis of 10 subjects receiving Ad5-GUCY2C-PADRE demonstrates proof-of-concept that GUCY2C is immunogenic in humans and that GUCY2C-directed vaccination is safe. Moreover, the presence of GUCY2C-specific antibody and CD8+ T-cell, but not CD4+ T-cell, responses is consistent with selective CD4+ T-cell tolerance observed in mouse models. These data establish GUCY2C as a safe and immunogenic target for immunotherapy in cancer patients.

Trial registration

ClincialTrials.gov identifier NCT01972737.

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